



Attention improvement to transcranial alternating current stimulation at gamma frequency over the right frontoparietal network: a preliminary report

Short Communication

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Corresponding author:

Gerald Tramontano;
Email: gtramontano@neuroci.com

Tien-Wen Lee and Sergio Almeida contributed equally to this research as co-first authors.

Tien-Wen Lee, Sergio Almeida and Gerald Tramontano

The NeuroCognitive Institute (NCI) Clinical Research Foundation, Mount Arlington, NJ, USA

Abstract

Applying transcranial alternating current stimulation (tACS) at 40 Hz to the frontal and parietal regions, either unilaterally (left or right) or bilaterally, can improve cognitive dysfunctions. This study aimed to explore the influence of tACS at gamma frequency over right fronto-parietal (FP) region on attention. The analysis is based on retrospective data from a clinical intervention. We administered test of variables of attention (TOVA; visual mode) to 44 participants with various neuropsychiatric diagnoses before and after 12 sessions of tACS treatment. Alternating currents at 2.0 mA were delivered to the electrode positions F4 and P4, following the 10–20 EEG convention, for 20 mins in each session. We observed significant improvement across 3 indices of the TOVA, including reduction of variability in reaction time ($p = 0.0002$), increase in d-Prime (separability of targets and non-targets; $p = 0.0157$), and decrease in commission error rate ($p = 0.0116$). The mean RT and omission error rate largely remained unchanged. Artificial injection of tACS at 40 Hz over right FP network may improve attention function, especially in the domains of consistency in performance, target/non-target discrimination, and inhibitory control.

Significant outcomes

- Transcranial alternating current stimulation (tACS) at 40 Hz applied to F4 and P4 EEG lead positions may enhance attention in diverse neuropsychiatric conditions.
- The tACS protocol comprised 12 sessions, each lasting 20 minutes, with a current of 2 mA.
- Significant improvements were observed in attention consistency, target/non-target discrimination, and inhibitory control.

Limitations

- The results of this preliminary report may be influenced by practice effects.
- Double-blind, sham-controlled studies with well-defined participant selection criteria are needed to validate the reported efficacy.

Introduction

Cortical oscillations at various frequencies have been linked to diverse cognitive functions. For instance, working memory and semantic memory functions have been, respectively, associated with power changes in the theta and upper alpha bands (Klimesch, 1999; Brzezicka *et al.*, 2019). Gamma rhythms have been associated with the functioning of extensive brain networks and cognitive processes such as attention, perceptual grouping, memory, and working memory (Fell *et al.*, 2002; Herrmann *et al.*, 2010; Brookes *et al.*, 2011; Lundqvist *et al.*, 2018). With the introduction of transcranial alternating current stimulation (tACS), it becomes possible to inject artificial oscillation into the brain and study its causal influence on neural rhythmicity and cognition.

Correspondent with neuroanatomical understanding, tACS at theta over anterior frontal and medial temporal and tACS at gamma over occipitoparietal regions lead to improvement in working memory task performance (Park *et al.*, 2022; Wischniewski *et al.*, 2024; Manippa *et al.*, 2024a). The tACS at theta/gamma ranges with anterior/posterior montages may improve episodic memory (Varastegan *et al.*, 2023), while the theta-gamma cross-frequency tACS targeting the prefrontal cortex may enhance visuomotor learning (Diedrich *et al.*, 2024). The



tACS at gamma frequency over right parietal and left temporoparietal regions may, respectively, modulate endogenous attention and auditory spatial attention (Hopfinger *et al.*, 2017; Wostmann *et al.*, 2018). The promising potential of gamma tACS in addressing mild cognitive impairment (MCI) and early stages of Alzheimer's disease (AD) has been suggested (Manippa *et al.*, 2024b). Positive evidence regarding the application of tACS to other neuropsychiatric conditions, such as dyslexia, anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD), is beginning to accumulate (Dallmer-Zerbe *et al.*, 2020; Lee *et al.*, 2024).

The clinical effects of tACS appear to be frequency- and region-specific as briefly summarised above. It is noteworthy, however, that sometimes tACS may be detrimental to neuropsychological performance. For example, prefrontal gamma modulation may impair working memory (Wischniewski *et al.*, 2024), and beta tACS may reduce motor cortex excitability (Zaghi *et al.*, 2010). Our recent report suggested that tACS may desynchronise underlying neural oscillation (Lee and Tramontano, 2024). It is thus imperative to empirically examine if a specific tACS protocol is beneficial. It is acknowledged that attention function engages broad neural substrates, relatively right-lateralised for visuospatial processing, particularly fronto-parietal (FP) network (Shipp, 2004; Thiebaut de Schotten *et al.*, 2011). To the best of our knowledge, the influence of gamma tACS over right FP regions on the attention function has never been specifically examined. The importance of investigating transcranial electrical stimulation (tES) on attention cannot be overstated, as attention is essential for the effective execution of other cognitive processes. If tACS does indeed influence attention, it would impact the neuropsychological interpretation of pertinent research.

Among the frequency bands of brain waves, we are particularly interested in gamma, given its coupling with downward spectra (delta to beta), co-bursts with beta in volitional control, close relevance to attention, and its roles in cognitive impairment in various neurocognitive conditions (Fell *et al.*, 2002; Fan *et al.*, 2007; Foster and Parvizi, 2012; Goodman *et al.*, 2018). This study was designed to trace the changes in attention function via the test of variables of attention (TOVA) following 12 sessions of tACS treatment (Lark *et al.*, 2008).

Materials and methods

Participants

The research protocol centred on patients exhibiting attention and other cognitive deficits who underwent 40 Hz tACS treatment applied to the right frontal and parietal regions. Participants were recruited through our clinics and included patients who were referred for neuropsychiatric evaluation and treatment. A consent form was acquired for each patient before the commencement of treatment. We conducted a review of data collected from our clinics between 2018 and 2022, with prior approval from a private Review Board (Pearl IRB; <https://www.pearlirb.com/>). To be enlisted in this study, patients need to have a diagnosis characterised by cognitive deficits (e.g. ADHD and MCI), or have a chief complaint of cognitive decline. Forty-four cognitively impaired patients were identified who underwent full tACS treatment as well as pre- and post-treatment TOVA assessments. Individuals with epilepsy, skull defects, intracranial electrodes, brain lesions, vascular clips or shunts in the brain, cardiac pacemakers, or other implanted biomedical devices, as well as those who are pregnant or lactating, were deemed ineligible for tES

in accordance with safety guidelines (Antal *et al.*, 2017; Matsumoto and Ugawa, 2017). Participants were instructed to maintain their current treatments, including medications, without any dosage adjustments during the tES treatment.

Administration of tACS

We employed the FDA-approved neuromodulation device called Starstim-8, developed by Neuroelectronics, Inc. (Barcelona, Spain), to address cognitive deficits arising from different causes. The device utilises electrodes connected through wires to a rechargeable battery, delivering electric currents directly to the scalp and brain. Prior to attaching the electrodes, the scalp underwent a gentle cleansing with skin preparation gel. Subsequently, conductive gel was applied to facilitate proper electrode-to-scalp contact. These steps were essential to maintain optimal electrode contact and ensure that the impedance level remained below 5 k Ω (DaSilva *et al.*, 2011).

The montage of electrodes covered the right lateral side of the head at F4 and P4 positions in terms of the 10–20 EEG convention. The peak current intensity was 2.0 mA, with sinewave currents oscillating at 40 Hz and alternating between electrodes F4 and P4, see Figure 1A. The simulation of electric field distribution is illustrated in Figure 1B. During the neuromodulation session, the subjects were asked to practice computerised cognitive training games (<https://www.happyneuronpro.com/>). To familiarise patients with tES, we implemented a gradual dose escalation strategy during the initial three sessions. This strategy involved the following current levels: 1.0 mA for the first session, 1.5 mA for the second session, and 2.0 mA for the third session. Each stimulation session had a duration of 20 mins, commencing with a 1 min ramp-up phase and concluding with a 30 s ramp-down phase to minimise skin irritation. The 12 treatment sessions were completed over 3 weeks, with sessions interrupted by weekends.

TOVA administration

Within one week before the initial treatment and after the last neuromodulation session, TOVA was administered via the platform Inquisit (<https://www.millisecond.com/>). TOVA is an individually administered computerised test designed to evaluate attention and impulse control in both normal and clinical populations (Lark *et al.*, 2008). This study exclusively reported findings related to the visual mode, although acknowledging the availability of both visual and auditory modes for assessment purposes. The visual TOVA presents two easily distinguishable geometric figures (target and non-target) at the centre of the computer screen. These stimuli appear for 100 milliseconds at intervals of 2000 milliseconds. Participants are instructed to respond to the target stimulus as rapidly as possible. During the first half of the test (stimulus infrequent condition), the target stimulus is presented in 22.5% of the trials ($n = 72$), whereas during the second half (stimulus frequent condition), it appears in 77.5% of the trials ($n = 252$). By manipulating the ratio of target to non-target stimuli, the design allows investigating the impact of varying response demands on the performance. Lumping together all the trials, this preliminary report focuses on five overarching indices: mean reaction time (RT), variability of RT, d-Prime (an indicator of the discriminability between target and non-target), commission errors, and omission errors. The TOVA manual provides age- and gender-matched norms (mean and standard deviation) so that the severity of impairment before treatment can be appraised by the converted z-scores.

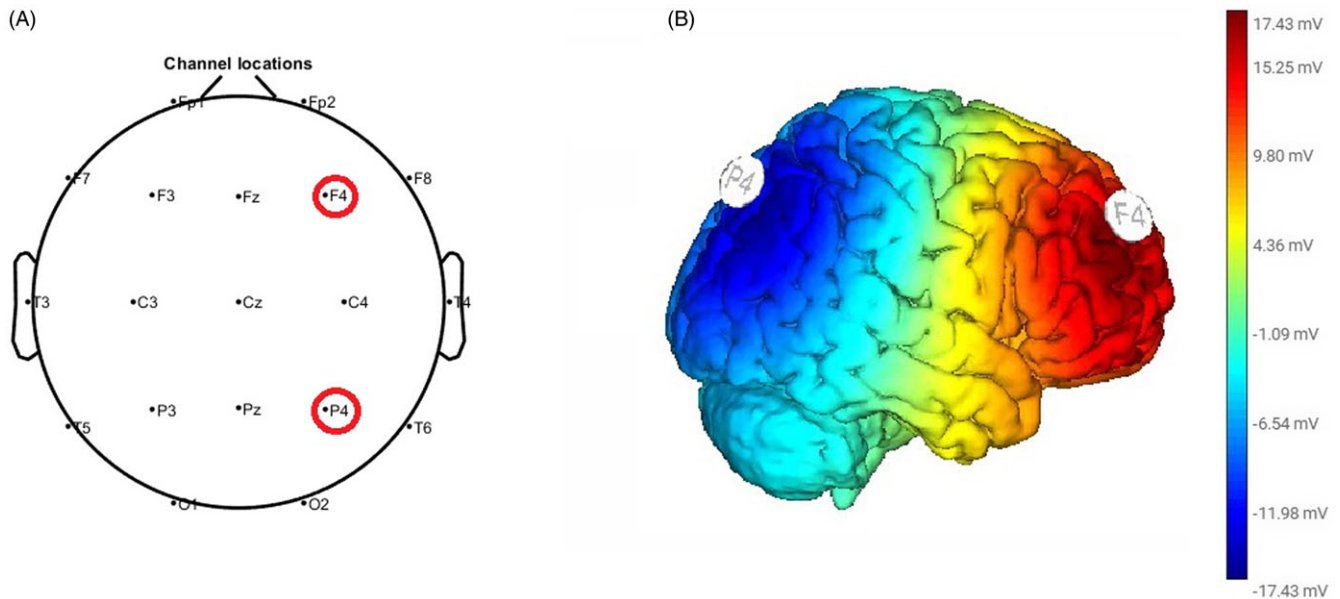


Figure 1. (A) An illustration of the F4 and P4 positions on the scalp. (B) simulation of tACS at 40 Hz over right FP regions.

Results

The age of the 44 patients ranged from 6.2 to 70.3 years (median 19.2), with a mean \pm SD of 25.1 ± 17.6 years. The average education was 9.42 years (SD = 5.4). Among them, there were 28 males and 16 females. All patients tolerated the maximum tES current at 2.0 mA. Their diagnoses include ADHD ($n = 13$), mild to moderate intellectual disability (9), learning disability (4), autism (3), non-amnesic MCI (9), AD-MCI (2), traumatic brain injury (2), and mood disorder (2). The most common comorbidities for ADHD and non-amnesic MCI were learning disabilities (8 out of 13) and traumatic brain injuries (2 out of 9), respectively. At baseline, the average RT variability and d-Prime are worse than age-matched norms by z-scores 3.3 and 2.3, exceeding the cut-off z-score of 1.645 (RT variability; the 95th cumulative percentile). The z-score of the patient with the least affected attention was 1.46 (the 92.8th cumulative percentile), indicating that all analysed participants had impaired attention. Commission and omission errors are also higher than normal population (z-scores are absent due to deviations of the raw scores from a normal distribution), see Table 1 for detail. The results for the ADHD subgroup are summarised in Table 2, showing a statistical trend similar to that in Table 1. The concurrent psychotropic medications, maintained at consistent dosages throughout the treatment, are as follows: 7 patients were on antipsychotics, 3 on central stimulants, 8 on antidepressants, and 2 on anxiolytics. One-fourth (11 out of 44) of patients were receiving psychotropic medications. The side effects were minimal, with the most common being itching or tingling sensations, consistent with another tACS study we conducted (Lee *et al.*, 2024).

Discussion

tES has been widely applied as a tool for basic and clinical research (Guleyupoglu *et al.*, 2013). In addition to offering a research gateway to modulate brain rhythms and cognitive processes, studies have begun to support tACS as a treatment option for

neuropsychiatric conditions (Lee *et al.*, 2024; Manippa *et al.*, 2024b). Previous research has investigated the potential of tACS at the gamma range to ameliorate various cognitive dysfunctions, predominantly episodic memory and working memory (Park *et al.*, 2022; Varastegan *et al.*, 2023; Wischniewski *et al.*, 2024; Manippa *et al.*, 2024a). Relatively few studies have delved into its impact on attention function, primarily focusing on healthy volunteers (Hopfinger *et al.*, 2017; Wostmann *et al.*, 2018). In addition, tACS has also been reported to modulate the frontoparietal attention network and, consequently, influence emotional attention (Hu *et al.*, 2021). Using TOVA, we evaluated attention function changes subsequent to 12 treatment sessions of 2mA tACS at 40 Hz over right frontal and parietal regions, aiming to ameliorate cognitive deficits stemming from diverse diagnoses. Through the comparisons of post-treatment minus baseline TOVA indices, our results showed that the treatment protocol benefited several, not all, aspects of attention function, including reduction of variability in RT, decrease of commission error, and improvement in separability of target and non-target, that is, d-Prime. The mean RT and omission error rate largely remained unchanged.

Each of the five selected indices from TOVA addresses a different domain of attention function (Leark *et al.*, 2007). RT provides a general measure of processing speed and efficiency, whereas the variability of RT indicates sustained attention or the stability of performance. Commission and omission error rates, respectively, reflect impulsivity (tendency to respond to non-target stimuli) and attentional lapses (failure to respond to target stimuli). The former is relevant to deficits in response inhibition or inhibitory control and the latter to deficits in vigilance or sustained attention. Overall, our results implied that gamma tACS over right FP network may benefit the consistency in performance and inhibitory control but has little impact on processing speed and attentional lapses. It is not surprising that the mean RT was resistant to the impact of tACS since the task instruction requires the participants to respond as quickly as possible (p.3 in professional manual (Leark *et al.*, 2008)). The improvement in

Table 1. Paired t-tests of TOVA profiles before and after gamma tACS treatment

	Before (std)	After (std)	<i>t</i> value	<i>p</i> value	Case no
RT variability (ms)	207.4 (113.7)	173.3 (97.3)	-4.12	0.000171	44
z-score	3.3 (2.7)	2.3 (2.3)			
RT (ms)	518.3 (156.1)	502.0 (157.4)	-0.93	0.356	44
z-score	1.6 (2.0)	1.4 (2.1)			
d-Prime	3.3 (1.2)	3.5 (1.1)	2.52	0.0157	43
z-score	-2.3 (1.7)	-2.2 (1.8)			
Commission (%)	9.6 (11.6)	6.6 (6.1)	-2.64	0.0116	44
Omission (%)	7.1 (8.0)	7.3 (11.8)	0.15	0.883	44

RT, reaction time; ms, millisecond; Z-scores are referred to the age-matched norm. One subject has missing data of d-Prime.

Table 2. Paired t-tests of TOVA profiles before and after gamma tACS treatment for ADHD

	Before (std)	After (std)	<i>t</i> value	<i>p</i> value	Case no
RT variability (ms)	272.1 (107.8)	215.4 (79.1)	-3.57	0.0038	13
z-score	4.0 (3.3)	2.4 (2.0)			
RT (ms)	579.6 (147.2)	569.7 (178.7)	-0.25	0.809	13
z-score	1.9 (1.4)	1.8 (2.1)			
d-Prime	2.9 (1.2)	3.3 (1.2)	1.73	0.109	13
z-score	-1.9 (1.4)	-1.6 (1.1)			
Commission (%)	10.4 (12.6)	7.6 (7.4)	-1.50	0.159	13
Omission (%)	9.3 (8.7)	9.0 (11.2)	-0.11	0.915	13

RT, reaction time; ms, millisecond; Z-scores are referred to the age-matched norm. One subject has missing data of d-Prime.

discriminating between targets and non-targets may be more closely linked to the decrease in commission errors rather than omission errors, which appeared to be unaffected by the treatment.

Complicated neural substrates participate in the attention functioning. For example, previous functional MRI research revealed that greater pre-stimulus brain activities in the default-mode network were associated with longer RT, and the BOLD responses in the posterior cingulate, left inferior frontal gyrus, and left middle temporal gyrus increased proportionally with RT (Tam *et al.*, 2015). In contrast, RT variability (intra-individual, as in TOVA) was predicted by the activity in the left anterior cingulate cortex (Johnson *et al.*, 2015). Error-related processing involved a broad neural matrix, including anterior cingulate cortex, pre-supplementary motor area, bilateral insula, thalamus, and inferior parietal lobule (Hester *et al.*, 2004). The neural mechanisms behind the therapeutic benefits of tACS are still being investigated. Nevertheless, with tES initiating low-resolution and wide-ranging neuromodulation (see Figure 1.), we posit that our tACS targeting the FP network may influence extensive neural substrates beyond those underneath F4 and P4, thereby modulating neural networks/nodes related to attentional function.

Our research samples were drawn from a heterogeneous mix of neuropsychiatric populations. In conjunction with sporadic reports supporting the efficacy of gamma tACS in enhancing attention (Hopfinger *et al.*, 2017; Wostmann *et al.*, 2018), we propose that gamma tACS may serve as a potential therapeutic intervention for a wide range of neuropsychiatric conditions,

irrespective of specific diagnoses. Including heterogeneous populations in the design may unveil the utility of tACS as a generic attention modulator. However, due to significant variations in the underlying mechanisms of attention and cognitive impairments across different neuropsychiatric disorders, the efficacy of tACS in enhancing attention and cognition is likely to vary among different diagnoses. Attention, a fundamental cognitive capacity, enables individuals to allocate resources and maintain focus on cognitive tasks to facilitate various cognitive functions. This study offers a new caveat for research on the use of gamma tACS to improve cognitive impairment, prompting consideration of whether the cognitive enhancement observed with tACS treatment is attributable to improved attention. Although this study includes only 12 sessions based on previous reports (Lee *et al.*, 2024; Manippa *et al.*, 2024b), extended maintenance treatment may be necessary to solidify the beneficial responses. We acknowledged that the results of this preliminary report could be contaminated by practice effects. In addition, including a severity criterion to better stratify participants may help in reducing heterogeneity and allow for more precise conclusions. Double-blind and sham-controlled research with well-defined participant selection guidelines is warranted to verify its efficacy and to clarify its role as an adjunct treatment for various conditions of attention and cognitive impairment.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/neu.2024.35>.

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Competing interests. All authors declare no conflicts of interest.

Ethical standards. This IRB-approved research analysed the databank collected from 2018 to 2022. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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